## REMARKS/ARGUMENTS

Claims 119-123 are pending in this application. The rejections to the presently pending claims are respectfully traversed.

### Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility." (Page 2 of the instant Final Office Action).

The Examiner maintains that the Applicants' assertion of utility is not substantial based on the teachings of Pennica *et al.*, Haynes *et al.*, Hu *et al.*, Chen *et al.*, Futcher *et al.*, and Gygi *et al.* The Examiner further points out to the reference by Li *et al.*, to state that "gene amplification does not predictably or even predominantly lead to increased transcription." (Page 14 of the instant Final Office Action).

### Arguments

Applicants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1097 polypeptide of SEQ ID NO:349 and the antibodies that binds it. Using a PCR-based assay, Applicants made the assertion that the gene encoding for PRO1097 was significantly amplified. The Declaration by Dr. Audrey Goddard explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample, relative to a normal sample, is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. The gene amplification data, thus, is sufficient to confer patentable utility to the instantly claimed antibodies to PRO1097 polypeptides.

Applicants also maintain, for the reasons provided in the previously filed responses, that Pennica *et al.*, Haynes *et al.*, Hu *et al.*, Chen *et al.*, Futcher *et al.*, and Gygi *et al.* do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. Applicants' arguments presented in the previously filed Response of January 10, 2007 and in the Preliminary Amendment of July 5, 2006 are hereby incorporated by reference in their entirety.

The Examiner relies on the teachings of Bieche *et al.* and Pitti *et al.* to allege that these authors did not use their data for diagnostic purposes, as in the instant application.

Applicants have discussed the references Pennica *et al.*, Bieche *et al.*, Pitti *et al.* and Hu *et al.*, in great detail in their Response dated January 10, 2007, and maintain their position regarding this matter. Applicants maintain that references Bieche *et al.* and Pitti *et al.* were presented to show the use of pooled DNA from normal, healthy donors as control was well-known and was widely utilized at the time of filing of the instant application. That the Bieche *et al.* and Pitti *et al.* used such controls for experimental purposes (and not for diagnostics, according to the Examiner) should bear no consequence to the fact that, pooled DNA controls were an acceptable control in the art at that time of filing of the instant application. Accordingly, the Examiner has not presented valid arguments or contrary evidence to show that the pooled control was not acceptable at the time of filing. Such a rejection is therefore improper.

The Examiner also states that she "cannot find any reason to suspect, that the protein encoded by the PRO1097 gene would confer any selective advantage on a cell expressing it" and that "there is no structure/ function analysis in the specification" (Page 8 of the instant Final Office Action).

Applicants respectfully traverse this rejection. Applicants submit that the request for "structure/ function data" is not a utility requirement. Neither is a showing of mechanism of action necessary for the utility requirement. Furthermore, Applicants note that selective advantage to cell survival is not the only mechanism by which genes impact cancer, and for this additional reason, this heightened requirement imposed by the Examine is improper according to the Utility standards set by the USPTO.

The Examiner further alleges that "(m)erely because aneuploidy may be an initial step in the *formation of cancer* does not equate with a substantial assertion of a diagnostic tool *for cancer* for the encoded PRO1097 protein." (Page 9 of the instant Final Office Action).

Again, Applicants need not explain the mechanism by which genes impact cancer, according to the Utility standards set by the USPTO. As discussed previously, even if the amplification observed for PRO1097 were due to aneuploidy (which Applicants do not concede to), the PRO1097 gene can at least be a marker for cancerous or pre-cancerous tissue or damaged tissue.

Moreover, Applicants would like to bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression." Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1097 polypeptide to refute Applicants' assertion of a correlation between mRNA levels and protein expression.

**Orntoft *et al.***

The Examiner maintains that the Orntoft *et al.*, reference is not persuasive because "the methodology used in the Orntoft reference is different from that of Applicant. (Page 13 of the instant Final Office Action).

The Orntoft reference was submitted by the Applicants to show that there was a gene dosage effect and teaches that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts." (See column 1, Abstract). Based on this reference and on several other references, Applicants have submitted that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method.

Applicants submit that the DNA encoding PRO1097 would have utility even if it were shown not to be in a gene cluster, because the instant specification has already determined that the PRO1097 DNA is amplified significantly compared to its control. Applicants have provided an expert Declaration (the Goddard Declaration) to support the significance of the values obtained in the gene amplification assay for PRO1097 DNA. Therefore, a utility rejection based on the premise that PRO1097 DNA may not be within an amplified cluster is not appropriate according to the utility standards.

**Li *et al.***

The Examiner cites new reference Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 14 of the instant Final Office Action).

Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma." (Page 2629, col. 1). For instance, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the case of PRO1097, as discussed in previously filed responses and in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold). The PRO1097 gene showed significant amplification of **2.313 fold to 2.346-fold** amplification in lung tumors and **2.114 fold to 2.532-fold** amplification in colon tumors, and thus fully meets this standard. It is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1097, would be expected to show a corresponding increase in transcript expression.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1097 polypeptides and the antibodies that bind to it, for example, in detecting over-expression or absence of expression of PRO1097. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides and the antibodies that bind to it. Hence, these data clearly support a role of PRO1097 as a lung and colon tumor marker.

Therefore, Applicants request that the Examiner reconsider this rejection and maintain that they have demonstrated utility for the PRO1097 polypeptide and antibodies thereof as diagnostic markers for human lung and colon tumors. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph, utility rejections should be withdrawn.

**Claim Rejections - 35 U.S.C. §112, First Paragraph - Enablement**

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, as allegedly "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Pages 15 of the instant Final Office Action).

Applicants respectfully traverse this rejection. Based on the discussions above under utility for the anti-PRO1097 antibodies in the diagnosis of lung or colon cancer, Applicants submit that the skilled artisan would not require undue experimentation to make and use the claimed invention.

Accordingly, Applicants request that this rejection be withdrawn.

## CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C30**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 24, 2007

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